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ORIGINAL ARTICLE

The potential impact of the hypovitaminosis D on metabolic complications in obese adolescents – Preliminary results

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Abstract

Introduction and objective. Vitamin D deficiency is common in obesity; however, its contribution in the development of metabolic complications remains uncertain. The aim of the study was to examine the relationships between vitamin D status and metabolic complications.

Materials and method. The results of blood pressure measurements, biochemical tests and ultrasound of the liver were compared in both groups. The study was conducted at the Children's University Hospital in Krakow, Poland. 30 obese adolescents (mean 13.23y.o.); 18 with 25OHD levels <20ng/mL, 12 with 25OHD>20 ng/mL.

Results. The vitamin D deficient group presented with significantly higher values of the diastolic blood pressure (125.9vs.115mmHg), uric acid level (384.7vs.301.5umol/L) and lower phosphorus level (1.4vs.1.65mmol/L), higher prevalence of arterial hypertension (44vs.8.3%), and liver steatosis (25vs.8.3%); lower, but not significantly, levels of fibroblast growth factor 23 and fibroblast growth factor 19.

Conclusions. Hypovitaminosis D in obese adolescents is associated with higher prevalence of arterial hypertension, liver steatosis, elevated serum uric acid and low phosphorus levels. The potential contribution of the fibroblast growth factor 23 and fibroblast growth factor 19 in these complications development needs further investigation.

Key words

obesity, hypovitaminosis D, uric acid, arterial hypertension, fibroblast growth factor 23, fibroblast growth factor 19, adolescents

INTRODUCTION

The global escalation of childhood obesity is a major public health issue, as excessive adiposity is the leading cause of metabolic and cardiovascular disease and their related mortality in adulthood. The main causes of this increase in cardiometabolic risk are a decrease in insulin sensitivity and compensatory hyperinsulinemia [1, 2, 3, 4]. A strong association between insulin resistance and an excess of fat tissue has been recognized for decades, but some details of its origin remain unclear to date. Undoubtedly there is a strong correlation between genetic background and environmental factors. Since it is not yet possible to modify the genetic background, it is essential to identify modifiable environmental factors. One of the most discussed in literature possible contributors of the obesity itself and its complications remains hypovitaminosis D. Many studies confirmed a high prevalence of vitamin D deficiency in obese patients, since both conditions are often associated. Approximately 60% of children and adolescents are overweight or obese in comparison to 20% of those who are non-obese subjects [1, 2, 3, 4]. However, an inverse correlation between body mass index (BMI), fat tissue content and vitamin D levels had been proved in many studies, and a recently published metaanalysis of 21 adult cohorts (up to 42,024 participants) revealed that higher a BMI leads to a lower vitamin D level. However, low vitamin D level does not contribute to an increase in the BMI [3]. These results confirm that hypovitaminosis D is rather a consequence, not a cause of obesity. From this point of view, low vitamin D may not be considered as an isolated condition, but rather the potential indicator of the risk of other metabolic complications in obese patients. Moreover, since puberty is a critical life-stage period characterized by rapid growth and development, the deficiency of vitamin D may be relative and difficult to diagnose, because there are no specific reference values and cut-off points for vitamin D level in adolescents. Recent studies had shown, that hypovitaminosis D might be not only one of the many obesity complications, but may be also a potential trigger factor of the consecutive metabolic disturbances. It had been shown, that low vitamin D level may be involved in the activation of a pro-inflammatory, pro-diabetic and atherogenic pathways in obese children [2].

The presented study is an attempt to compare selected parameters of the metabolic assessment in obese patients with hypovitaminosis D and obese with normal 25OHD levels. The study is also the first attempt to assess a possible relationship between FGF23, FGF19 and vitamin D status in obese adolescents.

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OBJECTIVE

The aim of the study is to determine the possible relationship between hypovitaminosis D and specific metabolic consequences of obesity (lipid disorders, non-alcoholic liver steatosis and arterial hypertension) in adolescents. Additionally, determination of a possible relationship between FGF23, FGF19 and vitamin D status in obese adolescents was investigated.

MATERIALS AND NETHOD

The study included 30 obese adolescents (14 male and 16 female) at the age of pubertly (mean age: 13.23 years, 95%CI 12.64–13.8).

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a stadiometer (Harpenden, UK) and a balance scale. As the standard of references for normal BMI SDS, values from the local population were used. Pubertal development was assessed according to the Tanner scale – Tanner stage IV or V.

Systolic (SBP) and diastolic (DBP) blood pressure were measured 3 times, every 3 minutes, using a pneumatic sphygmomanometer. Mean values were counted from obtained measures. Arterial hypertension (HA) was defined as mean SBP and/or DBP over 95th percentile for age, height and gender.

Fasting levels of 25OHD were measured by high-performance liquid chromatography. Hypovitaminosis D was defined as 25OHD < 20 ng/mL (50 nmol/L). Fasting concentration levels of glucose, total cholesterol LDL cholesterol (LDLc); HDL cholesterol concentration (HDLc), triglycerides (Tgl), uric acid (UA), alanine aminotransferase (ALT), asparginian aminotransferase (AST), gamma-glutamylo transferase (GGT), calcium and phosphorus, were estimated in the fasting blood sample by the dry chemistry method with a Vitros 5.1.FF machine. Insulin concentrations were measured with immunoradiometric kits (BioSource Company Europe SA). HOMA IR was calculated using the formula: [fasting insulin level (μIU/mL) x fasting glucose level (mmol/L)]/22.5. Serum FGF23 levels were measured in a fasting blood sample by Human Intact FGF23 Enzyme-Linked ImmunoSorbent Assay (Immunotopics Inc. USA), a two affinity purified goat polyclonal antibodies to detect epitopes with the amino-terminal and the carboxyterminal portions of FGF23. Serum FGF19 levels were measured in a fasting blood sample by Human FGF19 Enzyme-Linked Immuno Sorbent Assay (ELISA) (BioVendor – Laboratorni medicina a.s., Czech Republic).

Ultrasonography was performed using Philips EnVisor unit with an 3.5 MHz scanhead.

Statistical analysis. To compare two sets of data, the t-Student test was employed for independent samples, and in the case of absence of normal data distribution – the two-sided Mann-Whitney U test was used. The level of significance was set at $p<0.05$. Calculations were performed using STATISTICA 10.0 PL.

The study was conducted according to the principles expressed in the Declaration of Helsinki, and approved by the Jagiellonian University Bioethical Committee (Decision No. KBET/38/B/2008). All participants and their parents signed informed consent.

RESULTS

Mean BMI value in the whole group was 32.5 kg/m2 [SD 4.85]; mean BMI SDS – 4.65 [SD 1.67]. There was no significant difference concerning BMI values in patients with normal and low 25OHD levels – 30.5 kg/m2 [SD 4.02] vs 33.8 kg/m2 [SD 5.12], and also BMI SDS values 4.07 [SD 1.3] vs 5.03 [SD 1.8] respectively (Table 1).

Table 1. Comparison of selected parameters in the metabolic assessment of obese patients with hypovitaminosis D, and obese patients with normal 25OHD levels

Parameters	Hypovitaminosis D n=18 mean (SD)	Normal vitamin D level n=12 mean (SD)	p value
Age [years]	13.7 (1.25)	12.6 (1.86)	0.09
BMI SDS	5.03 (1.8)	4.07 (1.3)	0.16
SBP [mmHg]	125.9 (11.1)	115 (15)	0.07
DBP [mmHg]	78.6 (11.5)	69 (10.1)	**0.04***
fasting glucose [mmol/L]	4.56 (0.48)	4.57 (0.57)	0.21
fasting insulin [IU/L]	21.9 (9.9)	18.1 (5.1)	0.5
HOMA IR	4.5 (2.3)	3.8 (1.1)	0.66
Total cholesterol [mmol/L]	4.32 (0.8)	4.7 (0.9)	0.37
LDLc [mmol/L]	2.6 (0.7)	2.9 (0.9)	0.34
HDLc [mmol/L]	1.1 (0.2)	1.2 (0.4)	0.98
Triglicerydes [mmol/L]	1.3 (0.54)	1.5 (0.64)	0.4
Uric acid [umol/L]	384.7 (66.8)	301.5 (80.7)	**0.01***
AST [IU/L]	26.7 (8.6)	25.2 (5.1)	0.88
ALT [IU/L]	34.8 (19.7)	29.3 (5.1)	0.5
GGT [IU/L]	27.1 (2.8)	18 (5.3)	0.9
Ca [mmol/L]	2.43 (0.14)	2.47 (0.07)	0.35
P [mmol/L]	1.4 (0.25)	1.65 (0.11)	**0.04***
FGF23 [pg/mL]	6.08 (2.83)	7.11 (2.88)	0.47
FGF19[pg/mL]	128.1 (65)	150 (15)	0.39

The mean 25OHD level was 19.78 ng/mL (95%CI 15.9–23.6). Hypovitaminosis D was recognized in 18 patients (60%; 10 girls and 8 boys). The vitamin D deficient group presented with significantly higher values of diastolic blood pressure (125.9 vs. 115 mmHg; p=0.04), uric acid level (384.7 umol/L vs. 301.5 umol/L; p=0.01), and lower phosphorus level (1.4 vs. 1.65 mmol/L; p=0.04). In patients with hypovitaminosis D mean values of: HOMA IR (4.5 vs. 3.8; p=0.66), ALT (34.8 vs. 29.3 IU/L; p=0.5) and GGT (27.1 vs. 18 IU/L; p=0.9), were higher, but the differences were not significant. Further analysis showed lower, mean FGF23 and FGF19 levels (6.08 vs.7.11; p=0.47; 128.1 vs. 150; p=0.39, respectively), but the differences were not significant. Detail comparison of the mean values of the selected biochemical parameters and blood pressure are shown in Table 1. More than 44% (8 of 18) of patients with hypovitaminosis D presented with arterial hypertension, while only one patient with normal vitamin D level had elevated SBP. Liver steatosis features in the ultrasound examination and was present in over 44% (8 of 18) of the patients with low, and in 25% (3 of 12) of the patients with normal vitamin D level.

DISCUSSION

Vitamin D deficiency, defined as serum concentration less than 20 ng/mL, is one of the most common nutrition-responsive medical conditions worldwide [1, 2, 3]. However, although the association between hypovitaminosis D and obesity is well-established, there is still uncertainty which one is the cause, and which one is a consequence, and what the health consequences of lower concentrations of vitamin D might be. In the literature, the suggested mechanisms associated with obesity include: low calcium and vitamin D intake, less skin exposure to the sun due to reduced outdoor activity, reduced activation and/or increased catabolism than non-obese individuals, and sequestration of 25OHD in adipose tissue [3]. In children and adolescents who are overweight or obese it affects approximately 60% in comparison to 20% of non-obese subjects [1, 2, 3]. However, an inverse correlation between BMI, fat tissue content and vitamin D levels had been proved in many studies, and a recently published metaanalysis of 21 adult cohorts (up to 42,024 participants) revealed that higher BMI lead to lower vitamin D level; but in contradiction, low vitamin D level does not contribute to the increase in the BMI [3]. These results confirm that hypovitaminosis D is rather a consequence, not a cause of obesity. Epidemiological-pooled analysis of prospective observational studies of diverse populations demonstrates that hypovitaminosis D is associated with a slight risk of cardiovascular events [4, 5, 6, 7]. The decrease of the vitamin D level has also been associated with higher blood pressure levels, as already shown in many prospective studies, as well as meta-analyses of observational studies [5, 6]. The results of the presented study confirm that both systolic and diastolic blood pressure in patients with hypovitaminosis D were higher, and for the diastolic blood pressure the difference was significant (125.9 vs. 115 mmHg; p=0.04). Moreover, the incidence of arterial hypertension among obese patients with vitamin D deficiency was higher than in peers with normal vitamin D level (44% vs. 8.3%). Low vitamin D level was also associated with an elevated uric acid concentration level. An association between vitamin D deficiency and hyperuricemia in obese adolescents has not been reported; however, a significant association between vitamin D insufficiency and elevated uric acid was recently found in postmenopausal women [8]. This novel observation seems to be particularly interesting since it had been proved that an elevated uric acid level is a significant and independent predictor of the development of the arterial hypertension, especially in young individuals, and metabolic syndrome in the future [9, 10]. These findings may suggest that low vitamin D level is not only one of the complications of the obesity, but it can be involved in the development of other metabolic complications. The relationship between low vitamin D and elevated uric acid, and subsequent cardiovascular complications, is currently the subject of many studies. The results of the studies published to date allow only speculation about the potential mechanism and need confirmation by the future investigations. It is suggested that vitamin D deficiency or decreased bioactivity can activate parathyroids to induce the release of parathyroid hormone (PTH). That, in turn, is considered to raise the uric acid level, but details of this mechanism remain unknown [9, 10, 11]. It is suspected that elevation of the uric acid might be associated with the fluctuations of the fibroblast growth factor 23 (FGF23) level [12, 13, 14]. FGF23 is a protein synthesized by osteocytes that has been described as having a key role in the 'bone-kidney-parathyroid' axis and the regulation of phosphate-calcium-PTH and 1.25(OH)D metabolism. Recent studies have pointed to the potential role of the FGF23 in the development of insulin resistance and its metabolic consequences. Previous research by the authos of the current has shown that FGF23 may play a key role in the early phase of decreased insulin sensitivity in obese adolescents [15, 16].

The results of the presented study show,that in young patients with obesity and hypovitaminosis D, without clinical signs or symptoms of kidney disease, the FGF23 levels were lower in comparison to individuals with normal 25OHD levels; however, the difference was not statistically significant. Interestingly, the group with low vitamin D level and lower FGF23 level presented with significantly higher concentration levels of uric acid. This observation does not confirm the results of the previously mentioned study performed in pediatric patients with chronic kidney disease, and preserved kidney function [13], and points to a different and more complex mechanisms in adolescents with obesity. In obese adolescents, a low vitamin D level may slightly increase PTH which, in turn, can activate 1 alpha-hydroxylase and subsequently increase the 1,25OHD level, which t may be a potential cause of the further decrease of the 25OHD level, leading to a vicious circle. Moreover, a moderate rise of the PTH level may decrease the phosphorus level, which is associated with the slight decrease of the FGF23 level, as shown in previous studies conducted in populations with normal kidney function [17].

The results of the presented study show higher, but not significant, values of the HOMA IR in patients with hypovitaminosis D (4.5 vs. 3.8, p=0.66). However, some larger studies confirmed the relationship between vitamin D deficiency and insulin resistance [19, 20]. Since FGF23 is strongly involved in calcium-phosphorus-vitamin D metabolic pathways, it is reasonable to suspect that its contribution to the development of insulin resistance may be related to vitamin D deficiency, which is also considered an insulin resistance risk factor. Moreover, recent studies conducted on mice indicate that insulin signaling, or fat metabolism disturbances in the genetically ablated FGF23 are mediated by vitamin D [19, 20, 21]. Some studies have pointed to the presence of low FGF23 levels in vitamin D deficiency; but this was not confirmed in larger groups [22]. These insights indicate the potential contribution of vitamin D to the development of insulin resistance in a novel way. The presented study is the first attempt to assess a possible relationship between FGF23 and vitamin D status in obese adolescents.

Another interesting observation, although also not statistically significant, is the elevation of liver enzymes levels, especially ALT and GGT, in patients with hypovitaminosis D (34.8 vs. 29.3 IU/L; p=0.5; 27.1 vs. 18 IU/; p=0.9 respectively). The ultrasound revealed liver steatosis in 44.4% of the patients with low, and in 25% with normal vitamin D levels. That confirms the results of the meta-analysis published recently by Eliades et. al., that revealed significantly decreased serum 25OHD concentrations in patients with non-alcoholic fatty liver disease (NAFLD), suggesting that vitamin D may play a role in the development of this condition [21]. On the other side, as native vitamin D is converted to 25OHD in the liver, it remains controversial whether low 25OHD level is a cause

or a consequence of liver function impairment. Nevertheless, additional analysis performed in our study showed lower concentration level of the fibroblast growth factor 19 (FGF19) in patients with hypovitaminosis D. Fibroblast growth factor 19 (FGF19) is a hormone released from the small intestine; recently, it has emerged as an endocrine regulator of glucose and lipid metabolism. The results of the presented study, although not statistically significant, need particular attention, since a decrease in fasting FGF19 is an independent risk factor for the development of NAFLD in obese adolescents [23, 24, 25]. Its relationship to vitamin D deficiency needs further investigation.

Although the group investigated in the presented study was relatively small, the very interesting and promising preliminary results obtained indicate the possible contribution of vitamin D deficiency in the development of metabolic obesity complications. The mechanisms of such contribution need further investigation.

CONCLUSIONS

Hypovitaminosis D in obese adolescents is associated with a higher prevalence of arterial hypertension, liver steatosis, elevated serum uric acid and low phosphorus levels. The potential contribution of the fibroblast growth factor 23 and fibroblast growth factor 19 in the development of these complications needs further investigation.

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